

**REMARKS/ARGUMENTS**

Claims 1-29 are pending in the captioned application. Applicants first confirm the election for prosecution of Group II, claims 13-27, drawn to a compound of formula III. Applicants hereby cancel the non-elected claims 1-12 and withdraw claims 28 and 29.

Applicants have amended claim 28. The claim is amended to only depend on claim 13, for the purpose of rejoining, once the composition claims are found allowable.

Claims 13-27 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the letter "F" is used in two different ways in the specification, as halogen and also as a substituent in formula III. The Examiner is of the opinion that this makes the claims confusing. In response, Applicants have amended the specification and claim 13. Applicants have replaced F with R<sub>x</sub>, where F is a substituent in formula III. Applicants submit that the claim rejection under 35 U.S.C. §112, first paragraph, should now be withdrawn. The claim rejection under 35 U.S.C. §112, second paragraph, is also moot in view of the amendments.

The claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lee et al. (US 5863727) in view of Burdette et al. (J.Amer.Chem.Soc., (2001), 123, 7831-41). Applicants respectfully disagree.

Applicants submit that Lee et al. relates to energy transfer (ET) fluorescent dyes, reagents incorporating the dyes and methods of use having the generic structure at column 4, lines 20-33 which can be linked to other dyes through the R14 (or 4') position. However, Applicants assert that Lee et al. does not describe ET dyes in which both R11 (or 5') and R14 positions are utilized for coupling to another (acceptor) dye or where the R11 and R14 positions are utilized for coupling to an acceptor dye and another group such as a target bonding group. Thus Lee et al. does not specifically disclose molecules in which there are two aminomethyl groups (in the R11 and R14 positions, respectively).

Applicants submit that Burdette et al. relates to fluorescent sensors for detecting  $\text{Zn}^{2+}$ , of the type shown in structures 4 and 5 (pages 7836 and 7835 respectively). The Zinpyr sensors described by Burdette et al. have quantum yields of 0.38 and 0.25 in their non-coordinated states. The quantum yields increase to 0.87 and 0.92 when they are complexed with zinc (page 7836, left column). This change in fluorescence is therefore an indicator of zinc. It is noted that the response is zinc selective ( $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  produce no change and transition metal ions  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Fe}^{2+}$  and  $\text{Mn}^{2+}$  quench the fluorescence).

Applicants submit that Burdette et al. does not disclose a bis-aminomethyl fluorescein - rather the molecule disclosed is a 4',5'-bis[bis(2-pyridylmethyl)aminomethyl

derivative of fluorescein. This compound is necessary to provide the requisite number of coordinating sites for zinc. Applicants submit that Burdette et al. did not contemplate a structure of a bis-aminomethyl derivative because it would not be suitable for coordinating zinc. Burdette et al. also refers to quenching of the fluorescence from benzylic amines (page 7837, column 2) and it appears from Figure 3 that these molecules are very sensitive to changes in pH.

By contrast, Applicants submit that the 4'- and 5'-aminomethyl functionalities of the present invention are employed as suitable reactive groups for coupling to other dyes or biological molecules. When derivatized (note that  $R_1$  can be H) as such they form amides (see e.g. Example shown in Scheme 1).

The Examiner states that there is motivation to combine the teachings of Lee et al. with that of Burdette et al., because Burdette's compounds have fluorescence property. Applicants respectfully disagree. Applicants submit that Burdette et al. teaches tertiary amine derivatives of fluorescein which are pH sensitive. As discussed above, these compounds only have a fluorescence property when complexed with zinc (and by protonation of the tertiary amines, Figure 3). The compounds appear to be unsatisfactory as fluorescent indicators with any other metal tested. Applicants submit that it is clear from Burdette et al. that the fluorescence response of these dye compounds is  $Zn^{2+}$ -selective. Many first-row transition metals, in fact, quench the fluorescence. Therefore, a


skilled person in the field would not be motivated by Burdette et al. Applicants content that no motivation is provided by Burdette et al. for the combination with Lee et al., for the claimed invention.

It is contended that Burdette et al. does not render claims 13-27 obvious when considered with the teachings of Lee et al.

Applicants respectfully assert that the claims are in allowable form and earnestly solicit the allowance of pending claims.

Respectfully submitted,

GE Healthcare Bio-Sciences Corp.

By:   
Yonggang Ji  
Reg. No.: 53,073  
Agent for Applicants

GE Healthcare Bio-Sciences Corp.  
800 Centennial Avenue  
P. O. Box 1327  
Piscataway, New Jersey 08855-1327

Tel: (732) 980-2875  
Fax: (732) 457-8463

I hereby certify that this correspondence is being uploaded to the United States Patent and Trademark Office using the Electronic Filing System on July 18, 2007.

Signature: 

Name: \_\_\_\_\_

Melissa Leck